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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re U.S. Patent Application | ) | |
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| GOLDMANN, Helmut | ) | |
| | ) | |
| Serial No. 10/521,455 | ) | |
| | ) | Atty. Dkt. 26569U |
| For: IMPLANT WITH LONG-TERM ANTIBIOTIC ACTION | ) | |
| | ) | |
| | ) | |

DECLARATION UNDER 37 C.F.R. 1.132

Commissioner for Patents
Washington, DC 20231

Sir:

NOW COME the undersigned and declare that:

1. I, Helmut Goldmann, a citizen of Germany, having a post office address of Risibergstrasse 5, 78532 Tuttlingen.

2. I am [explain credentials in no more than about 5 lines – cv can be attached – identifying expertise in the medical implant arts is helpful];

3. I am the sole inventor of the subject matter of U.S. Patent Application Serial No. 10/521,455, and I am aware of and familiar with the Office Action dated June 24, 2008 wherein claims 18, 25, 27, and 32-34 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,296,863 to Trogolo et al. in view of U.S. Patent No. 6,530,951 to Bates et al.;

4. I am aware that regarding the Trogolo reference, the Examiner maintains the position that the following are disclosed: a vascular prosthesis for replacement of hollow organs with antibiotic long-term action with a basic structure which defines the form of the prosthesis and which defines the form of the prosthesis and which is made substantially non-absorbable or only slowly

absorbable material, with metallic silver situated on the polymer material and underneath the coating. Additionally, the Examiner maintains that Trogolo discloses the prosthesis porosity.

5. Based upon my understanding and expertise, it is clear that that Trogolo et al. discloses only ionic silver and not elemental silver as instantly claimed.

6. I am further aware that regarding the Bates reference the Examiner maintains the position that Bates teaches an implantable medical device having thin layers of elemental silver utilized for their antibacterial properties.

7. I am aware the main independent claim, i.e., is directed to silver which is exclusively elemental silver. And that further, the layered structure of the present implant provides for an antibiotic long-term effect with a characteristic initial high silver release after implantation. Neither of these features are made obvious by the combination of cited references.

8. In support of these statements, comparison tests have been presented in the instant specification. Specifically, see the published application paragraphs [0017] – [0023], which are reproduced and further discussed below.

EXAMPLE 1

[0017] Double-velour knitted prostheses of polyester are clamped in a rotatable clamp device so that they hang freely as a bundle of parallel tubes with spaces between them. The clamp device is introduced into a vacuum chamber suitable for carrying out the IBAD technique, the vascular prostheses being vapor-deposited with silver and at the same time bombarded with argon ions. The coating operation is conducted until a silver layer thickness of 1300Å is reached on the outside of the vascular prostheses or the fibers located there. If so desired, a primary coating can be effected by vapor-deposition of other metals. Silver is also forced into the pores or interstices between the fibers of the vascular prostheses, so that the fiber surfaces are coated at these locations too. However, the layer thickness is less there because of the "shadow effect" in the vapor-deposition.

[0018] The vascular prostheses coated in this way are removed from the clamp device and then impregnated in the usual manner with absorbable material at least on their outside, sealing off the porous structure. This impregnation can be done in the usual way with collagen, in which partial crosslinking with glutaraldehyde is effected. Preference is given to a likewise known coating with gelatin which is crosslinked with diisocyanate. As has been mentioned, bioactive substances can be introduced into the coating solution in order to develop the biological activity during the later absorption of the layer.

[0019] Determination of the amount of silver on the vascular prostheses (still without absorbable layer) has revealed that the proportion of silver relative to the total weight of the metallized prosthesis lies in the range of from 0.4 to 0.8% by weight. The proportion of silver depends inter alia on the porosity of the basic structure of the vascular prosthesis. Close-knitted structures have a lower percentage proportion of silver than more porous structures. Moreover, the penetration of the porous implant with silver can be influenced by the way in which the method is carried out, for example by moving the implants during vapor-deposition, by guiding the streams of vapor and gas in a particular way, etc. If, for example, an inner coating of tubular prostheses with silver is also desired, silver vapor can also flow through the inside of the prostheses during the coating operation. Turning the prosthesis round prior to a repeated vapor-deposition also leads to an inner coating.

[0021] A vascular prosthesis according to Example 1, but not yet provided with the absorbable impregnation layer, was placed in phosphate buffer (pH 7.4) at 37° C.; the phosphate buffer was changed daily and the silver content in the previous phosphate buffer sample was determined. The test extended across a period of 365 days. The silver content in the removed phosphate buffer was initially 35 microgram/l and then fell rapidly, and then after 50 days slowly (15 microgram/l), and after 365 days it was ca. 5 microgram/l.

[0022] Under the same conditions, a vascular prosthesis according to Example 1 was examined which was coated with an absorbable impregnation layer of gelatin crosslinked with diisocyanate. Although no silver was added to the gelatin, a high content of silver in the range of ca. 70 to 80 microgram/l was initially found in the phosphate buffer, and although it decreased slightly it remained high until the absorbable layer had largely broken up. It was not until after about 50 days that the silver content in the phosphate buffer had fallen to the level shown after 50 days by the vascular prosthesis not provided with the impregnation coating, after which time the release of the silver ions into the phosphate buffer was essentially the same as in the vascular prosthesis without impregnation coating.

[0023] This comparison shows that the silver layer was attacked via the impregnation coating, and silver ions were released into the impregnation coating, and these then entered the phosphate buffer at an increased rate and in increased number. The vascular prosthesis provided with the impregnation layer thereafter showed a comparable release of silver ions, which means that the initial strong release of silver has no negative effect on the long-term action.

9. The comparison shows that an implant according to the main claim, and one comprised only of elemental silver and also having a layered structure is capable of an antibiotic long-term effect with an initial high silver release after implantation.

10. All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any parent issuing thereon. Further, declarant saith not.

10. WITNESS my signature below on the indicated date.

2008-11-14 Helmut Goldmann

Date Helmut Goldmann

# Curriculum Vitae

## Personal Details

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|---|---|
| Name: | Dr. rer. nat. Helmut Goldmann |
| Address: | Risibergstr. 5<br>D-78532 Tuttlingen |
| Nationality: | German |
| Date of birth: | 18.08.1954 |

## Education and Qualification

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| 1973 | High School Diploma |
| 1981 | Final examination: Chemistry / Biology<br>Johannes-Gutenberg University Mainz, Germany |
| 1987 | Dr. of Natural Science (Ph.D.)<br>Johannes-Gutenberg University Mainz, Germany |

## Employment History

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| 1988 – 1997 | Head of R&D Laboratory<br>B. Braun Melsungen AG |
| 1997 to present | Director R&D Surgical Vascular Products<br>Aesculap AG, Tuttlingen |

Tuttlingen, 2008-11-14

Helmut Goldmann

## Conference Presentation

- H. Goldmann:
  Silver Grafts in the situation of infection
  Silberprothesen in der Infektionssituation
  4. Mitteldeutscher Chirurgenkongress, Leipzig 2008

- H. Goldmann:
  Textile implants: Prevention of graft infection
  ATC '04, 31st Aachen Textile Conference, Aachen 2004

## Manuscripts Under Review

- Antimicrobial Protection of Vascular Grafts
  Silver Coating with or without Rifampicin Bonding?
  R. A. Lang, J. Wingender, M. Strathman, H. Goldmann, M. H. Kirschner
  J. Surg. Res.

## Published Papers

- Polyaxial Absorbable Polyester for Sealing
  Vascular Grafts
  J. Lindsey III, H. Goldmann, Ch. Merckle, D. Ingram, Sh. Shalaby
  8th World Biomaterials Congress
  Amsterdam 2008 (Poster, P-SAT-K-677)

- In vivo Examination of the Humoral Immune Response
  against an Absorbable Polymer for Coating of Vascular Grafts
  A. Hoene, U. Walschus, H. Goldmann, T. Ueberrueck, L. Wilhelm, M. Schlosser
  8th World Biomaterials Congress
  Amsterdam 2008 (Poster, P-THU-J-655)

- Evaluation of the biocompatibility of a new vascular prosthesis
  coating by detection of prosthesis-specific antibodies
  U. Walschus, H. Goldmann, T. Ueberrueck, A. Hoene, M. Schlosser
  J. Mater Sci: Mater Med, 19 (4), 1595-1600 (2007)

- In vitro conditions for accelerated hydrolysis of bioabsorbable fibers
  M. T. Truong, T. H. Barrows, H. Goldmann, R. Althaus, H. H. Füllgrabe
  Trans. 21st Meeting Soc. Biomaterials 1995, 436

- Bis-ferrocene derivatives of bridged calix(4)arenes: synthesis, X-ray crystal structure and electro-chemical properties
  J. Organomet. Chem. 421, 265 (1991)
  P. D. Beer, A. D. Keefe, V. Böhmer, H. Goldmann, W. Vogt, S. Lecocq, M. Perrin

- Structure of 5, 17-dimethyl-11, 23-dioctylcalix(4)arene:
  J. Crystallo. Spect. Res. 21, 69 (1991)
  F. Gharnati, M. Perrin, S. Rantsordas, H. Goldmann, V. Böhmer

- Control of Alkali Cation Complexation in Bridged Calix(4)arene Esters Induced by Small Conformational Changes.
  J. Org. Chem. 55, 2569 (1990)
  V. Böhmer, W. Vogt, H. Goldmann, M. A. McKervey, M. Owens, S. Cremin, E. M. Collins

- Bridged Calix(4)arenas: X-Ray Crystal and Molecular Structures and Spectroscopic Studies.
  J. Chem. Soc. Perkin Trans. 2, 1990, 1769
  V. Böhmer, H. Goldmann, W. Vogt, E. F. Paulus, F. L. Tobiason, M. J. Thielman

- The Synthesis of Double-Calixarenes
  Tetrahedron Lett. 30, 1391 (1989)
  V. Böhmer, H. Goldmann, W. Vogt, J. Vicens, Z. Asfari

- X-Ray Crystal and Molecular Structure of a Trimeric o-Quinone Methid Derived from 2,6-Dibromomethyl-4-methylphenyl
  J. Chem. Soc. Perkin Trans. 2, 1989, 2059
  C. Bavoux, M. Perrin, H. Goldmann, V. Böhmer

- A Series of Calix(4)arenes, Having Two Opposite p-Positions Connected by an Aliphatic Chain
  J. Am. Chem. Soc. 110, 6811 (1988)
  H. Goldmann, W. Vogt, E. Paulus and V. Böhmer

- The Crystal and Molecular Structure of Two Calix(4)arenes Bridged at the para Position
  J. Chem. Soc. Perkin Trans. II, 1987, 1609
  E. Paulus, V. Böhmer, H. Goldmann, W. Vogt

- Photo-CIDNP Studies on Calixarenes and Bridged Calixarenes
  J. Chem. Soc. Chem. Commun., 1987, 1358
  V. Böhmer, H. Goldmann, R. Kaptein, L. Zetta

- The First Example of a New Class of Bridge Calixarene
  J. Chem. Soc. Chem. Commun., 1985, 667
  V. Böhmer, H. Goldmann, W. Vogt